PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference Moo1/02	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IN 02/00180	International filing date *(day/month/year)* 03.09.2002	Priority date *(day/month/year)* 03.09.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/40		
Applicant MOREPEN LABORATORIES LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.04.2004	22.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Johnson, C Telephone No. +49 89 2399-8287

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IN 02/00180

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-16 as originally filed

Claims, Numbers

1-22 received on 05.04.2004 with letter of 02.05.2003

Drawings, Figures

1-3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 7, 8(part),9(part),19

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 7,8(part),9(part),19 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 9(part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-6,8-18,20-22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6,8-18,20-22
Industrial applicability (IA)	Yes:	Claims	1-6,8-18,20-22
	No:	Claims	

2. Citations and explanations

see separate sheet

I. Basis of the report

No support has been found in the originally filed application for the melting point given in present claim 7, hence this claim does not appear to fulfil the requirements of Article 41(2) PCT. No opinion will therefore be given on this claim. Furthermore, the stipulation that the temperature of step a) in claims 8 and 9 is in the range of ambient to reflux temperature does not appear to be disclosed in the originally filed application. Claims 8 and 9 have therefore been examined as if the amendment to step a) had not been made.

III. Non-establishment of opinion

In the process of claim 9, it would appear that the desired calcium salt can only be obtained if the metal hydroxide used is calcium hydroxide (the lactone itself is not acidic, hence it cannot be introduced as the calcium salt). The search and examination have been performed on this basis.
Claim 19 is not clear - the proportion of alkaline earth metal hydroxide added is defined as being "50 times preferably 10 times of the starting compound more preferably in 1:1 ratio". It appears that the claim is presenting 3 different alternatives. None of these alternatives is illustrated in the examples (all examples appear to use 0.73 equivalents of calcium hydroxide, assuming the "lactone form of atorvastatin calcium" means the lactone form of atorvastatin - the lactone itself is not acidic, thus it cannot be the calcium salt). As this claim is neither clear, nor supported, it has not been examined.

V. Reasoned statement

Reference is made to the following documents:
D1: WO-A-0243732
D2: WO-A-02051804

Novelty

D1 discloses an atorvastatin calcium designated Form VI which is prepared by dissolving Form I in acetone and adding water to obtain a precipitate (see ex. 1). The resulting crystalline form appears to have the same properties as that described in the present claims. The X-ray powder diffractograms of the present polymorph, shown in present Figure 2 and that of the polymorph of D1, shown in Figure 1 of this document are identical, except that the present diffractogram has poorer resolution. Every single peak which the applicant has stated is disclosed in D1 but is not present in the applicant's disclosure can be clearly seen in the X-ray diffractogram of the presently claimed compound. The fact that the applicant has

only listed the most intense peaks in the claims does not alter the fact that additional peaks are present in the diffractogram. The applicant has provided no X-ray diffractograms which do not contain these peaks. The applicant further argues that there are no split or duplet peaks in the present X-ray pattern although such peaks are present in that of D1. This difference is however clearly caused by the poorer resolution of the present spectrum, rather than by a different crystal structure.

This disclosure destroys the novelty of claims 1-6, 8, 10-17 and 20-22, hence these claims do not fulfil the requirements of Article 33(2) PCT.

D2 discloses a process which involves dissolving the lactone form of atorvastatin in a mixture of an organic solvent and water, adding calcium hydroxide and isolating the crystallized atorvastatin calcium (see example 8b and claim 15). These process steps appear to anticipate claims 9, 18 and 19, although the product obtained is different. Thus, either these claims are not novel over D2, or they do not contain all the technical features necessary to obtain the desired product, in which case there is an insufficient disclosure. The applicant has argued that the solvents and the proportions of ingredients used are substantially different from those in D2. As the process of claims 9 and 18 does not specify the solvents used, except insofar as they are organic or aqueous, and does not mention proportions at all, this argument is without merit in establishing novelty for these claims.
Claims 9 and 18 do not fulfil the requirements of Article 33(2) PCT.

Inventive step
In view of the lack of novelty of claims 1-6, 8-18 and 20-22, these claims cannot be considered inventive and hence do not fulfil the requirements of Article 33(3) PCT.

Industrial applicability
Claims 1-6, 8-18 and 20-22 fulfil the requirements of Article 33(4) PCT.

CLAIMS

We Claim:

1. Atorvastatin calcium Form VI or hydrates thereof.

2. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having characterized by the following X-ray powder diffraction pattern expressed in terms of the 2 theta, d -spacings, and relative intensities with a relative intensity of > 15% measured on a Shimadzu XRD-6000 with copper K radiation of lamda 1.5406°A:

2θ	D	Relative intensity (>15%)
3.7365	23.4584	23.0
7.7200	11.4425	36.0
8.6985	10.1574	74.0
10.2185	8.6497	57.0
12.5933	7.0234	19.0
17.9103	4.9485	47.0
18.3600	4.8283	20.0
19.4031	4.5710	100.0
20.2800	4.3753	29.0
20.8200	4.2630	48.0
22.5122	3.9463	24.0
25.5848	3.4923	25.0

3. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having.

X-ray powder diffraction peaks at about 3.7, 8.6, 10.2, 18.o and 20.9 degrees at 2-θ and one large peak at 19.5 degree 2-θ.

4. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having characterized by the following solid state C^{13} nuclear magnetic resonance spectrum (NMR) wherein chemical shift is expressed in parts per million (PPM):

δ (ppm)
21.898
24.294
27.767
29.368
33.939
38.275
42.836
45.980
68.932
71.266
73.617
119.357
122.987
131.214
137.515
162.696
169.066
179.540
186.890
190.640

5. Crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having solid state C^{13} NMR signals at about 162.689ppm, 169.066ppm, 179.54ppm, 186.89ppm, and 190.64ppm.

6. Crystalline Form VI atorvastatin calcium contains up to 8 moles of water per mole of atorvastatin calcium.

7. Crystalline Form VI atorvastatin calcium is trihydrate.

8. A process for the preparation of crystalline Form VI atorvastatin calcium **both hydrate and anhydrous states,** [R-(R*, R*)]-2-(4-flurophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (2:1) having formula as shown in fig. 1 of the drawing accompanying this specification which comprises:

a) dissolving calcium salt of any form of atorvastatin in an **organic solvent such as** aliphatic ketone to get clear solution of atorvastatin salt,

b) optionally removing impurities,

c) adding demineralised water,

d) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

9. A process for the preparation of new polymorphic crystalline Form VI of atorvastatin calcium,[R-(R*, R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula of Fig. 1 which comprises:

a. dissolving lactone form of atorvastatin in an organic solvent preferably aliphatic ketone to get a clear solution,

b. adding an aqueous solution of alkaline solution of earth metal hydroxide and demineralised water under stirring,

c. isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

10. A process of claim 8 wherein the atorvastatin calcium used is amorphous or crystalline Form I, II, III, IV, & V of atorvastatin calcium or mixture thereof.

11. A process of claim 8 wherein the atorvastatin calcium used is in anhydrous or hydrate state containing up to 9 water molecules.

12. A process of claim 8 wherein an organic solvent used is selected from aliphatic ketones having 1 to 3 carbon atoms.

13. A process of claim 8 and 10 wherein the aliphatic ketones used are acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, preferably acetone.

14. A process of claim 8 wherein the organic solvent used is 100 times preferably 15 times more preferably 10 times of the starting compound.

15. A process of claim 8 wherein the dissolution is carried out by heating the suspension of atorvastatin calcium in an organic solvent to the reflux temperature of the solvent used preferably above 40 and below 80^0C more preferably 40 to 50^0C.

16. A process of claim 8 wherein the impurities are removed by filteration.

17. A process of claim 8 wherein the demineralised (DM) water used is 100 times preferably 10 times more preferably 5 times of the starting compound.

18. A process of claim 8 wherein DM water is added drop wise **maintaining the temperature** .

19. A process of claim 9 wherein the alkaline earth metal hydroxide used is calcium hydroxide.

20. A process of claim 9 wherein the aqueous solution of earth metal hydroxide is preferably added at elevated temperature preferably above 40^0C and below 80^0C more preferably at 40 to 50^0C.

21. A process of claim 9 wherein the alkaline earth metal hydroxide added is 50 times preferably 10 times of the starting compound more preferably in 1:1ratio.

22. A process of claims 8 & 9 wherein the cooling is effected slowly to a temperature in the range of –20°C to 20° (room temperature) preferably in the range of 15 to 20°C to effect crystallization. The cooling may be effected @ of 2 to 3°C.

23. A process of claims 8 & 9 wherein the isolation is carried out by conventional methods such as filtration, vacuum filtration, decantation, centrifugation.

24. A process of claims 8 & 9 wherein the drying is effected by known means like vacuum tray drier, rotacon vacuum drier, and at a temperature above 50 and below 80^0C, preferably at 55^0C for 12 to 30 hours.

AMENDED CLAIMS

[received by the International Bureau on 08 May 2003 (08.05.03);
original claims 1 to 24 replaced by amended claims 1 to 22; (5 pages)]

1. A **crystalline** Form VI atorvastatin calcium or hydrates thereof **having characterized by the X-ray powder diffraction pattern following 2 θ values measured using a Shimadzu XRD-6000 with copper K radiation of λ1.5406°A and with a relative intensity of > 15%**
3.7365, 7.7200, 8.6985, 10.2185, 12.5933, 17.9103, 18.3600, 19.4031, 20.2800, 20.8200, 22.5122, and 25.5848

2. A crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having X-ray powder diffraction peaks at about 3.7, 18.0, and 20.9 degrees at 2-θ and **large** peaks at **8.6, 10.2,** and 19.5 degree 2-θ.

3. A crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having characterized by the following solid state C^{13} nuclear magnetic resonance spectrum (NMR) wherein chemical shift is expressed in parts per million (PPM):

δ (ppm)
21.898
24.294
27.767
29.368
33.939
38.275
42.836

REPLACED BY ART 34 AMDT

45.980
68.932
71.266
73.617
119.357
122.987
131.214
137.515
162.696
169.066
179.540
186.890
190.640

4. A crystalline Form VI atorvastatin calcium or hydrates thereof of claim 1 having solid state C^{13} NMR signals at about 162.689ppm, 169.066ppm, 179.54ppm, 186.89ppm, and 190.64ppm.

5. A crystalline Form VI atorvastatin calcium of claim 1 contains up to 8 moles of water per mole of atorvastatin calcium.

6. A crystalline Form VI atorvastatin calcium of claim 1 contains up to 3 moles of water per mole of atorvastatin calcium.

7. **A crystalline Form VI atorvastatin calcium of claim 1 has melting point in the range of 177 to 182^{o}C**

REPLACED BY ART 34 AMDT

8. A process for the preparation of a crystalline Form VI atorvastatin calcium of claim 1 both hydrate and anhydrous states, [R-(R*, R*)]-2-(4-flurophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl amino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (2:1) having formula as shown in fig. 1 of the drawing accompanying this specification which comprises:

a) dissolving calcium salt of any form of atorvastatin in an organic solvent such as aliphatic ketone **preferably at a temperature in the range of ambient to reflux temperature** to get clear solution of atorvastatin salt,

b) optionally removing impurities,

a) adding demineralised water **maintaining the same temperature,**

d) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

9. A process for the preparation of new polymorphic crystalline Form VI of atorvastatin calcium,[R-(R*, R*)]-2-(4-fluorophenyl)-beta,delta-dihydroxy-5-(1-methylethyl)-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) having formula of Fig. 1 which comprises:

a) dissolving lactone form of atorvastatin in an organic solvent preferably aliphatic ketone **at a temperature in the range of ambient to reflux temperature** to get a clear solution,

b) adding an aqueous solution of alkaline solution of earth metal hydroxide and demineralised water under stirring **maintaining the same temperature,**

c) isolating crystallized polymorphic Form VI of atorvastatin calcium and drying, if desired, to get required water of crystallization.

REPLACED BY ART 34 AMDT

10. A process of claims 8 & 9 wherein the atorvastatin calcium used is amorphous or crystalline Form I, II, III, IV, & V of atorvastatin calcium or mixture thereof.

11. A process of claims 8 & 9 wherein the atorvastatin calcium used is in anhydrous or hydrate state containing up to 9 water molecules.

12.A process of claims 8 & 9 wherein an organic solvent used is selected from aliphatic ketones having 1 to 3 carbon atoms.

13.A process of claims 8, 9 and 12 wherein the aliphatic ketones used are acetone, methyl ethyl ketone, diethyl ketone, methyl propyl ketone, preferably acetone.

14.A process of claims 8 & 9 wherein the organic solvent used is 100 times preferably 15 times more preferably 10 times of the starting compound.

15.A process of claims 8 & 9 wherein the dissolution is carried out by heating the suspension of atorvastatin calcium in an organic solvent to above 40 and below 80^{0}C more preferably 40 to 50^{0}C.

16.A process of claims 8 & 9wherein the impurities are removed by filtration.

17.A process of claims 8 & 9 wherein the demineralised (DM) water used is 100 times preferably 10 times more preferably 5 times of the starting compound.

18.A process of claim 9 wherein the alkaline earth metal hydroxide used is calcium hydroxide.

REPLACED BY ART 34 AMDT

19.A process of claim 9 wherein the alkaline earth metal hydroxide added is 50 times preferably 10 times of the starting compound more preferably in 1:1ratio.

20.A process of claims 8 & 9 wherein the cooling is effected slowly to a temperature in the range of –20°C to 20° (room temperature) preferably in the range of 15 to 20°C to effect crystallization. The cooling may be effected @ of 2 to 3°C.

21.A process of claims 8 & 9 wherein the isolation is carried out conventional methods such as filtration, vacuum filtration, decantation, centrifugation.

22.A process of claims 8 & 9 wherein the drying is effected by known means like vacuum tray drier, rotacon vacuum drier, and at a temperature above 50 and below 80^0C, preferably at 55^0C for 12 to 30 hours.

REPLACED BY ART 34 AMDT